REMARKS

The last paragraph of the office action states that the rejection is final. However, the first page of the office action and the PAIR system indicates that the rejection is non-final. Because all the rejections are new, and because the amendments did not necessitate the new rejections, applicants believe that the non-final status is appropriate.

The prior office action indicated that claims 26, 38, and 115 were allowable if rewritten in independent form. Applicants accepted this judgment, cancelling all other claims and amending the claims to independent format. However, the last page of the office action indicates that the amendments necessitated the finality of the rejection. Applicants surmise that the indication that the rejection is final on the last page was added in error and should not have been used. Confirmation of the non-finality is respectfully requested.

New claims 122-123 have been added that recite that the polypeptide comprising an MHC Class I-binding epitope of mesothelin is from 8 to 25 residues in length. This is supported at paragraph 44 of the specification. New claims 124-125 recite that the polypeptide is a fusion polypeptide. This is supported at paragraph 44. New claim 126 recites that the polypeptide consists of the recited epitopes.

The Rejection of Claim 26, 38, and 115 Under 35 U.S.C. §103(a)

The U.S. Patent and Trademark Office rejects claims 26, 38, and 115 as obvious over Weiskirch, in view of Argani and Quan. The first two references have been previously cited and previously applied to claims of the application, but not to claims 26, 38, and 115. Quan is newly cited.

Weiskirch is cited by the patent office as teaching the delivery of a *Listeria monocytogenes* construct that expressed full-length or truncated nucleoprotein of influenza virus. Weiskirch is further cited as teaching that an MHC class I response to the influenza virus was induced in mice.

Argani is cited by the patent office as teaching that mesothelin is expressed in a variety of cancers types. The U.S. Patent and Trademark Office further points out a literature-reviewing statement by Argani, "Jaffee et al. have recently demonstrated that cell-mediated immunotherapy can be safe and effective in patients with pancreatic cancer (20)."[1]

Quan is cited by the patent office as teaching that surgical excision is traditional for solid tumors, but that other therapeutic modalities are included in the standard of care.

The Patent Office concludes from these disparate teachings that the exciting findings of the present invention would have been obvious. The present invention provides a method of treating pancreatic cancer that provides a long-lasting response in a class of patients. Pancreatic cancer is one of the most refractory of cancers. As Argani teaches, "These patients [pancreatic cancer patients] are usually asymptomatic until the tumor has reached an advanced stage, and most patients are not curable with existing therapy." Page 3866, column 2, lines 1-3. The overall 5-year survival rate is less than 5 %. (Jaffee et al., *J. Clin. Oncol. 19,* 145-156, 2001) No currently available treatments affect 2 year survival for patients with locally advanced and metastatic disease. (*Ibid.*)

The MPEP at §2143.02 guides: "A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007); Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.,* 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P.*

[1] The cell-mediated immunotherapy taught in reference (20) of Argani is *not* a genetically engineered bacterium as recited in the claims, but rather two human pancreatic tumor cell lines derived from clinical samples. See Jaffee et al., *J. Clin. Oncol. 19,* 145-156, 2001. The safety and efficacy of the latter does not suggest anything about the properties or use the former.

Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950) (emphasis added). The mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007). The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) The rejection of claims 26, 38, and 115 fails because one of skill in the art at the time the invention was made would have had no reasonable expectation of success, and because the results are far better than could have been predicted.

The data in Table 2 of the specification show that for human patients that did not generate a DTH[2] response to mesothelin the average survival time was 18.5 months. In contrast, the patients that did generate such a response survived for greater than 60 months. This is a remarkable improvement in the survival of patients with an otherwise grim prognosis. The data in Figure 11 show similarly remarkable results in a mouse model. Under conditions where none of the mice survived beyond 20 days post-challenge, 60 % of the mice inoculated with a mesothelin expressing construct survived greater than 90 days post-challenge. Thus the life-prolonging effect of an immune response to mesothelin is robust. Due to the general inability in the art to treat this disease effectively, these clinical and laboratory results are certainly unexpected in their magnitude.

While Argani is quite strong in his extrapolation from his findings of overexpression of mesothelin in pancreatic adenocarcinoma to diagnostic uses ("The finding of mesothelin overexpression in pancreatic adenocarcinoma has immediate diagnostic applications"),[3] he is rather timid about the application of the findings to therapy ("Our findings raise the possibility that mesothelin may also be a rational target for cell-mediated immunotherapy for pancreatic cancer.")[4] Why would Argani be so hesitant about therapeutic use? First, as discussed above, pancreatic

[2] Delayed Type Hypersensitivity is an inflammatory response that develops 24 to 72 hours after exposure to an antigen that the immune system recognizes as foreign. This type of immune response involves mainly T cells rather than antibodies (which are made by B cells). Also called delayed-type hypersensitivity response. (National Cancer Institute, Dictionary of Cancer Terms)
[3] Page 3867, column 1, lines 1-2.
[4] Page 3867, column 2, lines 16-18.

cancers have been refractory to all efforts and modalities of treatment. Thus, no person of ordinary skill in the art would have expected successful therapy based only on a finding of overexpression of a marker. Second, those of skill in the art of cancer therapy were aware that overexpression of a marker does not indicate that the marker would be an effective anti-cancer target. Tumor biology is complex, and abundant expression is not enough to make a good target. The very well studied case of EGFR is instructive. EGFR is a marker which is overexpressed in colorectal cancers. Cetuximab is an inhibitor of EGFR. However, overexpression of EGFR does not correlate with response to cetuximab. See Pardoll Declaration at paragraph 11. "[P]atients whose tumors showed a high expression of EGFR derived no more benefit from cetuximab than those with a low expression of EGFR. Furthermore, even patients with tumors negative for EGFR might benefit from this drug. The latter result is intriguing because the only expected target of these highly specific antibodies is EGFR." Italiano et al., *Ann. Surg. Oncol. 15,* 649-654 at 650, 2008. This spurred Italiano to study the relationship of gene copy number to cetuximab efficacy. The results were equally puzzling: EGFR gene copy gain was not correlated with various measures of response. Italiano summarized: "Neither EGFR expression assessed by IHC nor *EGFR* gene copy number assessed by FISH were statistically significantly correlated with objective response rate, disease control rate, progression-free survival, and overall survival." Italiano, at 649.

Another example of complexity in assuming that overexpression of a marker makes it a good therapeutic target is described for head and neck squamous cell carcinoma (HNSCC). Despite the elevated expression of EGFR in these tumors, if a particular mutation (EGFRvIII) was present in the tumors, the efficacy of cetuximab was abrogated. Sok et al., *Clin. Cancer. Res. 12:* 5064-5073, at 5068, 2006. See Pardoll Declaration at paragraph 12. This provides another reason why one of ordinary skill in the art could not assume that overexpression of a marker is sufficient reason to expect therapeutic efficacy using the marker as a target.

Another reason why a person of ordinary skill in the art would not expect that a marker that is overexpressed in cancer would predictably be a good therapeutic target for tumors is immunological tolerance. "The majority of T cell-recognized tumour antigens in humans are encoded by genes that are also present in normal tissues. Low levels of gene expression in normal

cells can lead to the inactivation of high-avidity T cells by immunological tolerance mechanisms. As a consequence, low avidity T cell responses in patients are often inadequate in providing tumour protection." Morris et al., *Clin. Exp. Immunol. 131:* 1-7, 2003, at abstract. Typically, individuals are immunologically tolerant to normal tissue antigens. "Cancer vaccines targeting 'self' antigens that are expressed at consistently high levels by tumor cells are potentially useful in immunotherapy, but immunological tolerance may block their function." Leitner et al., *Nat Med. 9*:33-9, 2003. The reason for tolerance may be to prevent auto-immune reactions. "[R]ecent evidence suggests that mechanisms of tolerance that normally exist to prevent autoimmune disease may also preclude the development of an adequate antitumor response and that tumors themselves have the ability to thwart the development of effective immune responses against their antigens." Mapara et al., *J. Clin. Oncol. 22,* 1136-1151, at abstract. See Pardoll Declaration at paragraph 13. The ability to overcome immune tolerance was not predictable at the time of the invention, therefore the use of any particular normal tissue antigen as an immune target was not predictable.

Finally, the specification itself provides a compelling example of a marker which was found to be overexpressed in pancreatic cancers but which did not represent a good target for immunotherapy. Prostate stem cell antigen (PSCA) is a marker that Serial Analysis of Gene Expression (SAGE) demonstrated was expressed by pancreatic tumors at similar levels to mesothelin. See specification at paragraph [94]. However, PSCA did not elicit an immune response in the patients who demonstrated a delayed type hypersensitivity (DTH) response to autologous tumor cells after vaccination with an allogeneic GM-CSF-secreting pancreatic tumor vaccine. See specification at paragraph [106]. In contrast, mesothelin did elicit such a response; mesothelin-specific T cells were detected in the DTH responders. See specification at paragraph [101]. Despite similar overexpression of mesothelin and PSCA in pancreatic cancer, the whole-cell, pancreatic cancer vaccine induced no immune response to PSCA. Specification at [115]. One of ordinary skill in the art would have been aware that abundant expression is not enough to make a marker a good target for tumor therapy. See Pardoll Declaration at paragraphs 6-10.

For all these reasons, one of ordinary skill in the relevant art of tumor immunology would not have found that Argani's teaching of overexpression of mesothelin in various tumors would

predictably lead to its successful use as an immune target. This lack of predictability is reflected in Argani's own diffident statement.

The *prima facie* rejection of claims 26, 38, and 115 as obvious must also fail because there would have been no motivation to combine the mesothelin epitope with the *Listeria monocytogenes* delivery system. Argani mentions a cell-based system, but the cell-based system he mentions is a human tumor cell line, not a genetically engineered bacterium. A whole cell vaccine would not have provided motivation to combine the recited elements of *Listeria monocytogenes* and a mesothelin epitope based. No other reason has been articulated to support the rejection.

Please withdraw the rejection and pass the application to allowance.

Respectfully submitted,

Dated: November 13, 2009

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